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INTERNET COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C. 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 07 February 2000 (07.02.00)	
International application No. PCT/HU98/00054	Applicant's or agent's file reference 13199 KB
International filing date (day/month/year) 05 June 1998 (05.06.98)	Priority date (day/month/year)
Applicant KÓTAY NAGY, Péter et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

05 January 2000 (05.01.00)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

BEST AVAILABLE COPY

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Juan Cruz
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

From the INTERNATIONAL BUREAU

To:

ADVOPATENT
Office of Patent and Trademark
Attorneys
P.O. Box 11
H-1251 Budapest
HONGRIE

Date of mailing (day/month/year) 16 December 1999 (16.12.99)		IMPORTANT NOTICE	
Applicant's or agent's file reference 13199 KB			
International application No. PCT/HU98/00054	International filing date (day/month/year) 05 June 1998 (05.06.98)	Priority date (day/month/year)	
Applicant EGIS GYÓGYSZERGYÁR RT. et al			

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
AU,CN,EP,IL,JP,KP,KR,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CU,CZ,DE,DK,EA,EE,ES,FI,GB,GE,GH,GM,GW,ID,IS,
KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RI,SD,SF,SG,SI,
SK,SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZW
The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
16 December 1999 (16.12.99) under No. WO 99/64402

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ _____

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA		Date of receipt of DEMAND	
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 13199 KB	
International application No. PCT/HU98/00054	International filing date (day/month/year) 05 June 1998 (05.06.98)	(Earliest) Priority date (day/month/year) ---	
Title of invention PROCESS FOR THE PREPARATION OF A 3/2H/-PYRIDAZINE-4-SUBSTITUTED AMINO-5-CHLORO-DERIVATIVE			
Box No. II APPLICANT(S)			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) EGIS GYÓGYSZERGYÁR RT. Budapest, Keresztúri út 30-38., H-1106 Hungary		Telephone No.:	
		Facsimile No.:	
		Teleprinter No.:	
State (that is, country) of nationality: Hungary		State (that is, country) of residence: Hungary	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) KÓTAY NAGY, Péter Vác, Nagymező u. 73., H-2600 Hungary			
State (that is, country) of nationality: Hungary		State (that is, country) of residence: Hungary	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) SIMIG, Gyula Budapest, Hollósy Simon u. 25., H-1126 Hungary			
State (that is, country) of nationality: Hungary		State (that is, country) of residence: Hungary	
<input checked="" type="checkbox"/> Further applicants are indicated on a continuation sheet.			

Continuation of Box No. II APPLICANT(S)	
<i>If none of the following sub-boxes is used, this sheet should not be included in the demand.</i>	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i> BARKÓCZY, József Budapest, Szirom u. 4-6/B., H-1016 Hungary	
State <i>(that is, country)</i> of nationality: Hungary	State <i>(that is, country)</i> of residence: Hungary
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i> SZTRUHÁR, Ilona Budapest, Vak Bottyán u. 3., H-1191 Hungary	
State <i>(that is, country)</i> of nationality: Hungary	State <i>(that is, country)</i> of residence: Hungary
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i> BALÁZS, László Budapest, Baross u. 38., H-1088 Hungary	
State <i>(that is, country)</i> of nationality: Hungary	State <i>(that is, country)</i> of residence: Hungary
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i> DOMÁN, Imre Budapest, Mohács u. 18/B., H-1135 Hungary	
State <i>(that is, country)</i> of nationality: Hungary	State <i>(that is, country)</i> of residence: Hungary
<input checked="" type="checkbox"/> Further applicants are indicated on another continuation sheet.	

Continuation of Box No. II APPLICANT(S)	
<i>If none of the following sub-boxes is used, this sheet should not be included in the demand.</i>	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i> GREFF, Zoltán Budapest, Gyöngyvirág u. 8., H-1028 Hungary	
State <i>(that is, country)</i> of nationality: Hungary	State <i>(that is, country)</i> of residence: Hungary
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i> RÁTKAI, Zoltán Budapest, Morvai u. 19., H-1101 Hungary	
State <i>(that is, country)</i> of nationality: Hungary	State <i>(that is, country)</i> of residence: Hungary
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i> SERES, Péter Budapest, Rádda Barnen u. 6., H-1153 Hungary	
State <i>(that is, country)</i> of nationality: Hungary	State <i>(that is, country)</i> of residence: Hungary
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i> KARANCSI, Tamás Budapest, Attila u. 65., H-1013 Hungary	
State <i>(that is, country)</i> of nationality: Hungary	State <i>(that is, country)</i> of residence: Hungary
<input type="checkbox"/> Further applicants are indicated on another continuation sheet.	

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCEThe following person is ☒ agent ☐ common representativeand ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*ADVOPATENT Office of Patent and
Trademark Attorneys
Budapest, P.O.Box 11, H-1251
Hungary

Telephone No.:

(36-1) 201-1528

Facsimile No.:

(36-1) 201-1692

Teleprinter No.:

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.**Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION****Statement concerning amendments:***

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filedthe description ☒ as originally filed☐ as amended under Article 34the claims ☒ as originally filed☐ as amended under Article 19 (together with any accompanying statement)☐ as amended under Article 34the drawings ☐ as originally filed☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). (This check-box may be marked only where the time limit under Article 19 has not yet expired.)

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

☒ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purposes of international search.☐ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.**Box No. V ELECTION OF STATES**

The applicant hereby elects all eligible States (that is, all States which have been designated and which are bound by Chapter II of the PCT)

excluding the following States which the applicant wishes not to elect:

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|--------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | sheets |
| 6. other (<i>specify</i>) | : | sheets |

For International Preliminary Examining Authority use only

received not received

<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>

The demand is also accompanied by the item(s) marked below:

- | | |
|--|---|
| 1. <input checked="" type="checkbox"/> fee calculation sheet | 4. <input type="checkbox"/> statement explaining lack of signature |
| 2. <input type="checkbox"/> separate signed power of attorney | 5. <input type="checkbox"/> nucleotide and or amino acid sequence listing in computer readable form |
| 3. <input type="checkbox"/> copy of general power of attorney; reference number, if any: | 6. <input type="checkbox"/> other (<i>specify</i>): |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

KARÁCSONYI, Béla
Patent Attorney

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.

☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

PCT

FEE CALCULATION SHEET

Annex to the Demand for international preliminary examination

For International Preliminary Examining Authority use only

<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 20%;">International application No.</td> <td>PCT/HU98/00054</td> </tr> <tr> <td>Applicant's or agent's file reference</td> <td>13199 KB</td> </tr> </table>	International application No.	PCT/HU98/00054	Applicant's or agent's file reference	13199 KB	<div style="border: 1px solid black; height: 100px; width: 100%;"></div>
International application No.	PCT/HU98/00054				
Applicant's or agent's file reference	13199 KB				
Applicant EGIS GYÓGYSZERGYÁR RT. et al. Budapest, Keresztúri út 30-38., H-1106, Hungary					
Calculation of prescribed fees					
1. Preliminary examination fee EUR	<div style="border: 1px solid black; display: inline-block; padding: 2px 10px;">1533.-</div> <div style="border: 1px solid black; display: inline-block; padding: 2px 5px; margin-left: 5px;">P</div>				
2. Handling fee (<i>Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.</i>) EUR	<div style="border: 1px solid black; display: inline-block; padding: 2px 10px;">148.-</div> <div style="border: 1px solid black; display: inline-block; padding: 2px 5px; margin-left: 5px;">H</div>				
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box EUR	<div style="border: 1px solid black; display: inline-block; padding: 2px 10px;">1681.-</div>				
<div style="border: 1px solid black; display: inline-block; padding: 2px 10px;">TOTAL</div>					
Mode of Payment					
<input type="checkbox"/> authorization to charge deposit account with the IPEA (see below)	<input type="checkbox"/> cash				
<input type="checkbox"/> cheque	<input type="checkbox"/> revenue stamps				
<input type="checkbox"/> postal money order	<input type="checkbox"/> coupons				
<input checked="" type="checkbox"/> bank draft	<input type="checkbox"/> other (specify):				
Deposit Account Authorization (<i>this mode of payment may not be available at all IPEAs</i>)					
The IPEA/ _____ <input type="checkbox"/> is hereby authorized to charge the total fees indicated above to my deposit account.					
<input type="checkbox"/> (<i>this check-box may be marked only if the conditions for deposit accounts of the IPEA so permit</i>) is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.					
Deposit Account Number _____	Date (day/month/year) _____				
Signature _____					

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum)

Box No. I TITLE OF INVENTION

PROCESS FOR THE PREPARATION OF A 3/2H/-PYRIDAZINONE-4-SUBSTITUTED AMINO-5-CHLORO-DERIVATIVE

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

EGIS GYÓGYSZERGYÁR RT.

Budapest, Keresztúri út 30-38., H-1106

Hungary

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State (i.e. country) of nationality:

Hungary

State (i.e. country) of residence:

Hungary

This person is applicant for the purposes of:

☐ all designated States

☒ all designated States except the United States of America

☐ the United States of America only

☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

KÓTAY NAGY, Péter

Vác, Nagymező u. 73., H-2600

Hungary

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

Hungary

State (i.e. country) of residence:

Hungary

This person is applicant for the purposes of:

☐ all designated States

☐ all designated States except the United States of America

☒ the United States of America only

☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒ agent

☐ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

ADVOPATENT

Office of Patent and Trademark Attorneys

Budapest, P.O.Box 11, H-1251

Hungary

Telephone No.

(36-1) 201-1528

Facsimile No.

(36-1) 201-1692

Teleprinter No.

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

SIMIG, Gyula

Budapest, Hollósy Simon u. 25., H-1126

Hungary

This person is:

☐ applicant only☒ applicant and inventor☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

Hungary

State (i.e. country) of residence:

Hungary

This person is applicant for the purposes of:

☐ all designated States☐ all designated States except the United States of America☒ the United States of America only☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

BARKÓCZY, József

Budapest, Szirom u. 4-6/B., H-1016

Hungary

This person is:

☐ applicant only☒ applicant and inventor☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

Hungary

State (i.e. country) of residence:

Hungary

This person is applicant for the purposes of:

☐ all designated States☐ all designated States except the United States of America☒ the United States of America only☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

SZTRUHÁR, Ilona

Budapest, Vak Bottyán u. 3., H-1191

Hungary

This person is:

☐ applicant only☒ applicant and inventor☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

Hungary

State (i.e. country) of residence:

Hungary

This person is applicant for the purposes of:

☐ all designated States☐ all designated States except the United States of America☒ the United States of America only☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

BALÁZS, László

Budapest, Baross u. 38., H-1088

Hungary

This person is:

☐ applicant only☒ applicant and inventor☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

Hungary

State (i.e. country) of residence:

Hungary

This person is applicant for the purposes of:

☐ all designated States☐ all designated States except the United States of America☒ the United States of America only☐ the States indicated in the Supplemental Box☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

DOMÁN, Imre

Budapest, Mohács u. 18/B., H-1135

Hungary

This person is:

☐ applicant only☒ applicant and inventor☐ inventor only (If this check-box is marked, do not fill in below.)State (i.e. country) of nationality:
HungaryState (i.e. country) of residence:
HungaryThis person is applicant
for the purposes of:☐ all designated
States☐ all designated States except
the United States of America☒ the United States
of America only☐ the States indicated in
the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

GREFF, Zoltán

Budapest, Gyöngyvirág u. 8., H-1028

Hungary

This person is:

☐ applicant only☒ applicant and inventor☐ inventor only (If this check-box is marked, do not fill in below.)State (i.e. country) of nationality:
HungaryState (i.e. country) of residence:
HungaryThis person is applicant
for the purposes of:☐ all designated
States☐ all designated States except
the United States of America☒ the United States
of America only☐ the States indicated in
the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

RÁTKAI, Zoltán

Budapest, Morvai u. 19., H-1101

Hungary

This person is:

☐ applicant only☒ applicant and inventor☐ inventor only (If this check-box is marked, do not fill in below.)State (i.e. country) of nationality:
HungaryState (i.e. country) of residence:
HungaryThis person is applicant
for the purposes of:☐ all designated
States☐ all designated States except
the United States of America☒ the United States
of America only☐ the States indicated in
the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

SERES, Péter

Budapest, Rádda Barnen u. 6., H-1153

Hungary

This person is:

☐ applicant only☒ applicant and inventor☐ inventor only (If this check-box is marked, do not fill in below.)State (i.e. country) of nationality:
HungaryState (i.e. country) of residence:
HungaryThis person is applicant
for the purposes of:☐ all designated
States☐ all designated States except
the United States of America☒ the United States
of America only☐ the States indicated in
the Supplemental Box☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

KARANCSI, Tamás

Budapest, Attila u. 65., H-1013

Hungary

This person is:

☐ applicant only☒ applicant and inventor☐ inventor only (If this check-box is marked, do not fill in below.)State (i.e. country) of nationality:
HungaryState (i.e. country) of residence:
HungaryThis person is applicant
for the purposes of:☐ all designated
States☐ all designated States except
the United States of America☒ the United States
of America only☐ the States indicated in
the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

This person is:

☐ applicant only☐ applicant and inventor☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

State (i.e. country) of residence:

This person is applicant
for the purposes of:☐ all designated
States☐ all designated States except
the United States of America☐ the United States
of America only☐ the States indicated in
the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

This person is:

☐ applicant only☐ applicant and inventor☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

State (i.e. country) of residence:

This person is applicant
for the purposes of:☐ all designated
States☐ all designated States except
the United States of America☐ the United States
of America only☐ the States indicated in
the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

This person is:

☐ applicant only☐ applicant and inventor☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

State (i.e. country) of residence:

This person is applicant
for the purposes of:☐ all designated
States☐ all designated States except
the United States of America☐ the United States
of America only☐ the States indicated in
the Supplemental Box☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

Regional Patent

- ☒ AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | |
|--|--|
| <input checked="" type="checkbox"/> AL Albania | <input checked="" type="checkbox"/> LT Lithuania |
| <input checked="" type="checkbox"/> AM Armenia | <input checked="" type="checkbox"/> LU Luxembourg |
| <input checked="" type="checkbox"/> AT Austria | <input checked="" type="checkbox"/> LV Latvia |
| <input checked="" type="checkbox"/> AU Australia | <input checked="" type="checkbox"/> MD Republic of Moldova |
| <input checked="" type="checkbox"/> AZ Azerbaijan | <input checked="" type="checkbox"/> MG Madagascar |
| <input checked="" type="checkbox"/> BA Bosnia and Herzegovina | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia |
| <input checked="" type="checkbox"/> BB Barbados | <input checked="" type="checkbox"/> MN Mongolia |
| <input checked="" type="checkbox"/> BG Bulgaria | <input checked="" type="checkbox"/> MW Malawi |
| <input checked="" type="checkbox"/> BR Brazil | <input checked="" type="checkbox"/> MX Mexico |
| <input checked="" type="checkbox"/> BY Belarus | <input checked="" type="checkbox"/> NO Norway |
| <input checked="" type="checkbox"/> CA Canada | <input checked="" type="checkbox"/> NZ New Zealand |
| <input checked="" type="checkbox"/> CH and LI Switzerland and Liechtenstein | <input checked="" type="checkbox"/> PL Poland |
| <input checked="" type="checkbox"/> CN China | <input checked="" type="checkbox"/> PT Portugal |
| <input checked="" type="checkbox"/> CU Cuba | <input checked="" type="checkbox"/> RO Romania |
| <input checked="" type="checkbox"/> CZ Czech Republic | <input checked="" type="checkbox"/> RU Russian Federation |
| <input checked="" type="checkbox"/> DE Germany | <input checked="" type="checkbox"/> SD Sudan |
| <input checked="" type="checkbox"/> DK Denmark | <input checked="" type="checkbox"/> SE Sweden |
| <input checked="" type="checkbox"/> EE Estonia | <input checked="" type="checkbox"/> SG Singapore |
| <input checked="" type="checkbox"/> ES Spain | <input checked="" type="checkbox"/> SI Slovenia |
| <input checked="" type="checkbox"/> FI Finland | <input checked="" type="checkbox"/> SK Slovakia |
| <input checked="" type="checkbox"/> GB United Kingdom | <input checked="" type="checkbox"/> SL Sierra Leone |
| <input checked="" type="checkbox"/> GE Georgia | <input checked="" type="checkbox"/> TJ Tajikistan |
| <input checked="" type="checkbox"/> GH Ghana | <input checked="" type="checkbox"/> TM Turkmenistan |
| <input checked="" type="checkbox"/> GM Gambia | <input checked="" type="checkbox"/> TR Turkey |
| <input checked="" type="checkbox"/> GW Guinea-Bissau | <input checked="" type="checkbox"/> TT Trinidad and Tobago |
| <input type="checkbox"/> HU Hungary | <input checked="" type="checkbox"/> UA Ukraine |
| <input checked="" type="checkbox"/> ID Indonesia | <input checked="" type="checkbox"/> UG Uganda |
| <input checked="" type="checkbox"/> IL Israel | <input checked="" type="checkbox"/> US United States of America |
| <input checked="" type="checkbox"/> IS Iceland | <input checked="" type="checkbox"/> UZ Uzbekistan |
| <input checked="" type="checkbox"/> JP Japan | <input checked="" type="checkbox"/> VN Viet Nam |
| <input checked="" type="checkbox"/> KE Kenya | <input checked="" type="checkbox"/> YU Yugoslavia |
| <input checked="" type="checkbox"/> KG Kyrgyzstan | <input checked="" type="checkbox"/> ZW Zimbabwe |
| <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea | |
| <input checked="" type="checkbox"/> KR Republic of Korea | |
| <input checked="" type="checkbox"/> KZ Kazakhstan | |
| <input checked="" type="checkbox"/> LC Saint Lucia | |
| <input checked="" type="checkbox"/> LK Sri Lanka | |
| <input checked="" type="checkbox"/> LR Liberia | |
| <input checked="" type="checkbox"/> LS Lesotho | |

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- ☐
- ☐
- ☐

In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except the designation(s) of

The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)

Box No. VI PRIORITY CLAIM		Further priority claims are indicated in the Supplemental Box <input type="checkbox"/>	
The priority of the following earlier application(s) is hereby claimed:			
Country (in which, or for which, the application was filed)	Filing Date (day/month/year)	Application No.	Office of filing (only for regional or international application)
item (1) -	-	-	
item (2)			
item (3)			
Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required): <input type="checkbox"/> The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s): _____			
Box No. VII INTERNATIONAL SEARCHING AUTHORITY			
Choice of International Searching Authority (ISA) (If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used): ISA / _____			
Earlier search Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search, to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request: Country (or regional Office): _____ Date (day/month/year): _____ Number: _____			
Box No. VIII CHECK LIST			
This international application contains the following number of sheets: 1. request : 6 sheets 2. description : 38 sheets 3. claims : 10 sheets 4. abstract : 1 sheets 5. drawings : _____ sheets Total : 55 sheets		This international application is accompanied by the item(s) marked below: 1. <input type="checkbox"/> separate signed power of attorney 2. <input type="checkbox"/> copy of general power of attorney 3. <input type="checkbox"/> statement explaining lack of signature 4. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s): _____ 5. <input type="checkbox"/> fee calculation sheet 6. <input type="checkbox"/> separate indications concerning deposited microorganisms 7. <input type="checkbox"/> nucleotide and/or amino acid sequence listing (diskette) 8. <input type="checkbox"/> other (specify): _____	
Figure No. _____ of the drawings (if any) should accompany the abstract when it is published.			
Box No. IX SIGNATURE OF APPLICANT OR AGENT			
Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).			
KARÁCSONYI, Béla Patent Attorney			

For receiving Office use only	
1. Date of actual receipt of the purported international application:	2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority specified by the applicant: ISA /	6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid

For International Bureau use only
Date of receipt of the record copy by the International Bureau:

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International application No.

Applicant's or agent's
file reference

13199 KB

Date stamp of the receiving Office

Applicant

EGIS GYÓGYSZERGYÁR RT., Budapest, Keresztúri út 30-38., H-1106
Hungary

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE HUF 14000.- T

2. SEARCH FEE DEM 2200.- S

International search to be carried out by EPO

(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application contains 55 sheets.

first 30 sheets CHF 650.- b₁

25 x 15 CHF = 375.- b₂

remaining sheets additional amount

Add amounts entered at b₁ and b₂ and enter total at B . CHF . 1025.- B

Designation Fees

The international application contains designations.

11 x 150.- = 1650.- D

number of designation fees amount of designation fee
payable (maximum 11)

Add amounts entered at B and D and enter total at I . CHF . 2675.- I

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT P

5. TOTAL FEES PAYABLE

Add amounts entered at T, S, I and P, and enter total in the TOTAL box

TOTAL

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

☐ authorization to charge
deposit account (see below)

☒ bank draft

☐ coupons

☐ cheque

☐ cash

☐ other (specify):

☐ postal money order

☐ revenue stamps

DEPOSIT ACCOUNT AUTHORIZATION (this mode of payment may not be available at all receiving Offices)

The RO/ ☐ is hereby authorized to charge the total fees indicated above to my deposit account.

☐ is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

☐ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

Deposit Account Number

Date (day/month/year)

Signature

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

To: ADVOPATENT Office of Patent and Trademark Attorneys H-1251 Budapest HUNGARY
--

Date of mailing (day/month/year)	12/02/1999
-------------------------------------	-------------------

Applicant's or agent's file reference 13199 KB	FOR FURTHER ACTION See paragraphs 1 and 4 below
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International application No. PCT/HU 98/00054	International filing date (day/month/year) 05/06/1998
---	---

Applicant EGIS GYOGYSZERGYAR RT. et al.

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland
 Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.


☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer <div style="text-align: center; font-size: 1.2em;">John De Bruijn</div>
--	--

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 13199 KB	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/HU 98/00054	International filing date (day/month/year) 05/06/1998	(Earliest) Priority Date (day/month/year)
Applicant EGIS GYOGYSZERGYAR RT. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☐ Certain claims were found unsearchable (see Box I).

2. ☐ Unity of invention is lacking (see Box II).

3. ☐ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing

☐ filed with the international application.

☐ furnished by the applicant separately from the international application,

☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

☐ Transcribed by this Authority

4. With regard to the title, ☒ the text is approved as submitted by the applicant

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is:

Figure No. — ☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/HU 98/00054

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D237/22 C07D237/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 262 526 A (EGIS GYOGYSZERGYAR) 23 June 1993 cited in the application see claims 1,11	1,2
A	EP 0 054 946 A (CASSELLA) 30 June 1982 see claims; examples 1-7	1

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

3 February 1999

Date of mailing of the international search report

12/02/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Francois, J

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/HU 98/00054

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
GB 2262526	A	23-06-1993	HU 214320 B	02-03-1998
			AT 403282 B	29-12-1997
			AT 253592 A	15-05-1997
			AU 652304 B	18-08-1994
			AU 3031792 A	24-06-1993
			BE 1006223 A	14-06-1994
			CA 2085796 A	21-06-1993
			CH 684754 A	15-12-1994
			CN 1088578 A	29-06-1994
			DE 4243381 A	24-06-1993
			DK 152892 A	21-06-1993
			ES 2108595 A	16-12-1997
			FI 925807 A	21-06-1993
			FR 2685329 A	25-06-1993
			GR 92100570 A, B	31-08-1993
			HU 9500265 A	28-09-1995
			JP 5255276 A	05-10-1993
			NL 9202210 A	16-07-1993
			PL 297070 A	07-03-1994
			US 5395934 A	07-03-1995
			ZA 9209903 A	24-06-1993
EP 054946	A	30-06-1982	DE 3048487 A	29-07-1982
			AT 8991 T	15-09-1984
			AU 544386 B	23-05-1985
			AU 7870481 A	01-07-1982
			CA 1173033 A	21-08-1984
			CS 236683 B	15-05-1985
			CS 236665 B	15-05-1985
			DD 202013 A	24-08-1983
			DK 542881 A, B,	23-06-1982
			FI 813941 A, B,	23-06-1982
			GR 81382 A	11-12-1984
			HK 51485 A	12-07-1985
			IE 51985 B	13-05-1987
			JP 57128677 A	10-08-1982
			PT 74185 B	24-03-1987
			SU 1170970 A	30-07-1985
			SU 1151204 A	15-04-1985
			US 4532239 A	30-07-1985
			ZA 8108806 A	24-11-1982

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

ADVOPATENT
Office of Patent and
Trademark Attorneys
P.O. Box 11
H-1251 Budapest
HONGRIE

PCT

WRITTEN OPINION

(PCT Rule 66)

2000. 07. 17.

Date of mailing
(day/month/year)

17. 04. 00

Applicant's or agent's file reference

13199 KB

REPLY DUE

within 3 month(s)

from the above date of mailing

International application No.

PCT/HU98/00054

International filing date (day/month/year)

05/06/1998

Priority date (day/month/year)

05/06/1998

International Patent Classification (IPC) or both national classification and IPC

C07D237/22

Applicant

EGIS GYOGYSZERGYAR RT. et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain document cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 05/10/2000.

Name and mailing address of the international preliminary examining authority:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner

Fanni, S

Formalities officer (incl. extension of time limits)

Ambroa, J.R.

Telephone No. +49 89 2399 8012



I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

Description, pages:

1-38 as originally filed

Claims, No.:

1-18 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-18
Inventive step (IS)	Claims	1-18
Industrial applicability (IA)	Claims	

2. Citations and explanations

see separate sheet

ITEM V

Reference is made to the following documents:

D1: GB-A-2 262 526 cited in the application

D2: EP-A-0 054 946

NOVELTY

The subject matter of present claims 1-11 is novel over D1 mainly on account of the assembling of present compounds of formulae II (or VII) and VI during the synthesis of I, rather than compounds of formulae III and IV according to claim 11 from D1.

The subject matter of present claims 1-11 is novel over D2 mainly on account of the different regiochemistry of the 3(2H)-pyridazinone moieties involved.

Neither D1 nor D2 disclose 3-chloro substituted pyridazine derivatives. The 3, 5-trichloropyridazine derivative of formula IV disclosed by claim 14 is therefore novel over D1 and D2.

The subject matter of present claims 15-18 is novel over D1 mainly on account of the amino residues in position 3 of the 3(2H)-pyridazinone moieties, none of said residues having been disclosed by D1 (see the definition of A in formula I, claim 1 of D1).

The subject matter of present claims 15-18 is novel over D2, mainly on account of the different regiochemistry of the 3(2H)-pyridazinone moieties, the amino substituents being in position 5 in the compounds disclosed by D2. Furthermore, none of the present amino residues are disclosed by D2 (compare for instance, formulae II and III from present claims 15-18 with formulae I, IV and VI from claims 1 and 7 from D2).

The present subject matter therefore fulfil the requirement of article 33(2) PCT.

INVENTIVE STEP

D1 is considered to be the closest prior art and discloses 3(2H)-Pyridazinone

derivatives, including compounds according to the present formula I, and their medical application.

The problem underlying the present subject matters is considered to be the provision of an improved method for the synthesis of compounds according to formula I.

The problem has been solved, as shown by the comparison of present examples 1-5 with examples 1-7 from D1.

As stated in the description, the advantages of the present process over the one disclosed by D1 mainly reside in the higher regioselectivity, which is induced in the first step of the process, and the consequent possible separation of the regioisomers in an earlier and simpler purification step. On the other hand, there are no information in the prior art suggesting that the first step of the present process (namely the amination of 3, 4, 5-chloropyridazine) would lead to a general improving of the regioselectivity with respect to the process disclosed by D1.

Accordingly, a process involving a synthetic step which leads to compound IV by amination of 3, 4, 5-chloropyridazine could in principle be considered as inventive. This is however the case only for variant a_4 from present claim 1 and dependent claims 11-13 which refer to it.

For the variants which do not include the above mentioned synthetic step, namely variants a_1 - a_3 and b_1 - b_4 described in claim 1 as well as the dependent claims that refer to them, an inventive step cannot be acknowledged for the following reasons:

- i) variants a_1 - a_3 and b_3 - b_4 describe a known method for the synthesis of a tertiary amine by alkylation of a secondary amine via a nucleophilic substitution reaction;
- ii) variants a_2 - a_3 and b_4 describe known methods for the conversion of an ester or ether group into a better leaving group,
- iii) variants a_3 and b_2 - b_4 describe a known method for the conversion of 3-pyridazine into 3-pyridazone derivatives;

iv) variants b_1 - b_4 describe known methods for the deprotection of a secondary amine; All the above methods represent standard synthetic procedures or methods known as such. Therefore they represent merely some of the several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed.

**WRITTEN OPINION
SEPARATE SHEET**

International application No. PCT/HU98/00054

Thus the subject matter of claim 1, as well as the subject matter of dependent claims 2-10, which all refer to one of the variants a_1 - a_3 , do not fulfil the requirements of Article 33(3) PCT. Moreover, a unity of invention objection could be raised regarding the different variants according to the above mentioned claims.

An inventive step could be therefore acknowledged only for the subject matter of claims 11-13 (Article 33(3)PCT).

The compounds claimed in claims 14-18 are involved in at least some of the process described in claims 1-10. Said process being considered neither novel nor inventive, an inventive step could not be acknowledged for the subject matter of claims 14-18 (Article 33(3)PCT).

It is also pointed out that properties establishing an inventive step should extend to the whole of the scope claimed. Generic and open-ended expressions, such as "aryl", "alkanoyl", "aroyl" and "leaving group" are certainly not suited for this purpose, since it is inherently unlikely that substantially all of the embodiments claimed may be made or performed, i.e. provide compounds with the required properties.

2000 AUG 28

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

ADVOPATENT Office of Patent and
Trademark Attorneys
P.O. Box 11
H-1251 Budapest
HONGRIE

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)Date of mailing
(day/month/year)

24. 08. 00

Applicant's or agent's file reference
13199 KB

IMPORTANT NOTIFICATION

International application No.
PCT/HU98/00054International filing date (day/month/year)
05/06/1998Priority date (day/month/year)
05/06/1998

Applicant

EGIS GYOGYSZERGYAR RT. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 apmu d
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Authorized officer

Goeller, A

Tel. +49 89 2399-8013



L. 1885

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 13199 KB	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/HU98/00054	International filing date (day/month/year) 05/06/1998	Priority date (day/month/year) 05/06/1998
International Patent Classification (IPC) or national classification and IPC C07D237/22		
Applicant EGIS GYOGYSZERGYAR RT. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 05/01/2000	Date of completion of this report 24. 08. 00
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Fanni, S  Telephone No. +49 89 2399 8712

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/HU98/00054

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-38 as originally filed

Claims, No.:

1-18 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-18
	No:	Claims	
Inventive step (IS)	Yes:	Claims	11-18
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	1-18
	No:	Claims	

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/HU98/00054

2. Citations and explanations

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/HU98/00054

ITEM V

Reference is made to the following documents:

D1: GB-A-2 262 526 cited in the application

D2: EP-A-0 054 946

NOVELTY

The subject matter of present claims 1-11 is novel over D1 mainly on account of the assembling of present compounds of formulae II (or VII) and VI during the synthesis of I, rather than compounds of formulae III and IV according to claim 11 from D1.

The subject matter of present claims 1-11 is novel over D2 mainly on account of the different regiochemistry of the 3(2H)-pyridazinone moieties involved.

Neither D1 nor D2 disclose 3-chloro substituted pyridazine derivatives. The 3, 5-trichloropyridazine derivative of formula IV disclosed by claim 14 is therefore novel over D1 and D2.

The subject matter of present claims 15-18 is novel over D1 mainly on account of the amino residues in position 3 of the 3(2H)-pyridazinone moieties, none of said residues having been disclosed by D1 (see the definition of A in formula I, claim 1 of D1).

The subject matter of present claims 15-18 is novel over D2, mainly on account of the different regiochemistry of the 3(2H)-pyridazinone moieties, the amino substituents being in position 5 in the compounds disclosed by D2. Furthermore, none of the present amino residues are disclosed by D2 (compare for instance, formulae II and III from present claims 15-18 with formulae I, IV and VI from claims 1 and 7 from D2).

The present subject matter therefore fulfil the requirement of article 33(2) PCT.

INVENTIVE STEP

D1 is considered to be the closest prior art and discloses 3(2H)-Pyridazinone

derivatives, including compounds according to the present formula I, and their medical application.

The problem underlying the present subject matters is considered to be the provision of an improved method for the synthesis of compounds according to formula I.

The problem has been solved, as shown by the comparison of present examples 1-5 with examples 1-7 from D1.

As stated in the description, the advantages of the present process over the one disclosed by D1 mainly reside in the higher regioselectivity, which is induced in the first step of the process, and the consequent possible separation of the regioisomers in an earlier and simpler purification step. On the other hand, there are no information in the prior art suggesting that the first step of the present process (namely the amination of 3, 4, 5-chloropyridazine) would lead to a general improving of the regioselectivity with respect to the process disclosed by D1.

Accordingly, a process involving a synthetic step which leads to compound IV by amination of 3, 4, 5-chloropyridazine could in principle be considered as inventive. This is however the case only for variant a4 from present claim 1 and dependent claims 11-13 which refer to it.

For the variants which do not include the above mentioned synthetic step, namely variants a1-a3 and b1-b4 described in claim 1 as well as the dependent claims that refer to them, an inventive step cannot be acknowledged for the following reasons:

- i) variants a1-a3 and b3-b4 describe a known method for the synthesis of a tertiary amine by alkylation of a secondary amine via a nucleophilic substitution reaction (see, for example, claim 7 from D2. According to claim 7 and the examples of D2, the chlorine atom in position 4 is not affected during the nucleophilic reaction between compounds of formula IV and V according to claim 7 of D2. Furthermore, the equivalence in reactivity of the 4-chloro and the 5-chloro positions in 3-pyridazinones towards nucleophilic substitutions is disclosed by D1 as explained on page 3 of the present application);

- ii) variants a2-a3 and b4 describe known methods for the conversion of an ester or ether group into a better leaving group,

- iii) variants a3 and b2-b4 describe a known method for the conversion of 3-pyridazine into 3-pyridazone derivatives;

iv) variants b1-b4 describe known methods for the deprotection of a secondary amine (the hydrolysis of secondary amides in acidic medium is a well known process, see for instance J. March, *"Advance Organic Chemistry"*, 4th Edition, Wiley Ed., chapter 0-11, page 383);

All the above methods represent standard synthetic procedures or methods known as such. Therefore they represent merely some of the several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed. The arguments of the applicant that compounds of formula III are easily purified from their (undesired) 5-isomer, is of relevance only when the compound IV obtained from the reaction of V with 3-amino-1-propanol is used in the successive step without purification from the (undesired) IVa isomer. This synthetic strategy can be however considered covered only by variant a4.

Thus the subject matter of claim 1, as well as the subject matter of dependent claims 2-10, which all refer to one of the variants a1-a3, do not fulfil the requirements of Article 33(3) PCT.

An inventive step could be therefore acknowledged only for the subject matter of claims 11-13 (Article 33(3)PCT).

The compounds claimed in claims 14-18 are all considered to be essential features of the process described in variant a4 and claims 11-13. Said process being considered novel and inventive, an inventive step could be acknowledged for the subject matter of claims 14-18 (Article 33(3)PCT).

Since only the present variant a4 is considered as inventive, the question of unity of invention is not raised here, all the other variants claimed being not considered solutions for the given problem. It is however pointed out that if one or more of the claimed variants will be rendered inventive, the question of unity will have to be considered. It is furthermore pointed out that properties establishing an inventive step should extend to the whole of the scope claimed. Generic and open-ended expressions, such as "aryl", "alkanoyl", "aroyl" and "leaving group" are certainly not suited for this purpose, since it is inherently unlikely that substantially all of the

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/HU98/00054

embodiments claimed may be made or performed, i.e. provide compounds with the required properties.

In re the Application of: EGIS Gyógyszergyár Rt.
International Appln. No.: PCT/HU98/00054
International Filing Date: 05/06/1998
Title: PROCESS FOR THE PREPARATION OF A
3(2H)-PYRIDAZINONE-4-SUBSTITUTED
AMINO-5-CHLORO-DERIVATIVE
Agent's file reference: 13199 KB/NK
Authorized Officer: FANNI, S., Esq.

To.: EUROPEAN PATENT OFFICE
D-80298 Munich

By fax

Dear Sirs,

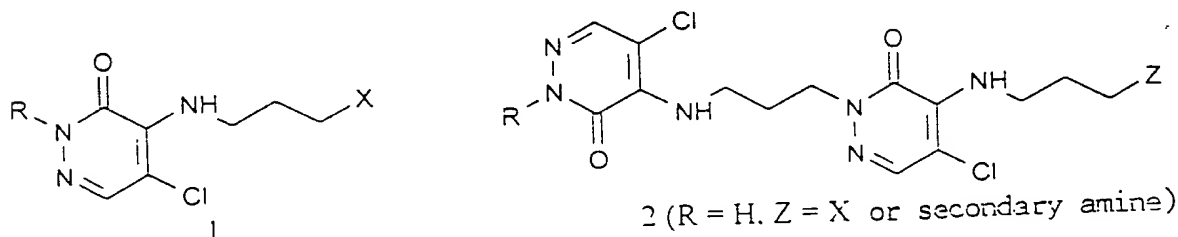
This response is to the Written Opinion of the International Preliminary Examining Authority mailed on 17. 04. 2000 having a reply due date of 17 July 2000 and extended until 17. August 2000 (hereinafter "Written Opinion").

I.

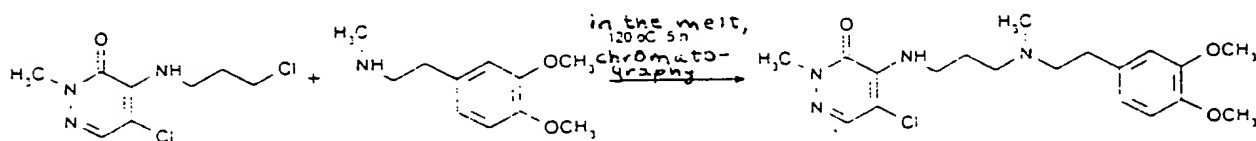
According to the Written Opinion reaction variants a₁-a₃ and b₃-b₄ are methods known per se for the synthesis of tertiary amines by the alkylation of secondary amines.

1) Reactions a₁-a₃

It is true that tertiary amines can be prepared by the alkylation of secondary amines. However, this is only relevant if the reaction is carried out by using pyridazinones of the general Formula (1) in which R is **other than hydrogen**. In the contrary case there is always a high probability of self-alkylation reaction and the formation of derivatives of two different types:

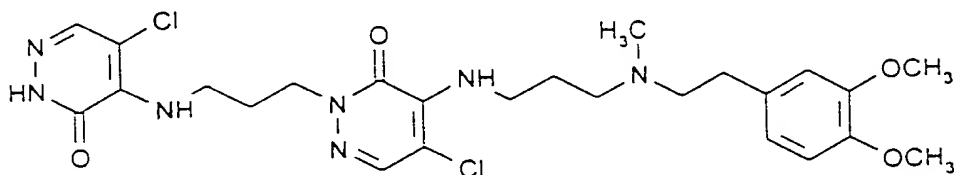


For 4-(ω-chloro-alkylamino)-pyridazinone-2-one derivatives only one single example is disclosed in prior art as an illustration of reactions of this type. This is Example 41 on page 29 of patent D1.



In this case the N-2 nitrogen of the pyridazinone ring bears a methyl substituent and therefore this nitrogen atom is protected against alkylation reactions. We

have carried out the reaction under the conditions disclosed in Example 41 of document D1 by performing the reaction in the melt at 120°C. It has been found that if the nitrogen atom N-2 bears a hydrogen atom, self-alkylation takes place on the N-2 nitrogen atom and a number of by-products are formed. A reaction mixture is obtained which can be purified only by substantial difficulties and the yields are drastically decreased. Thus e.g. a compound of the following Formula can be formed which is not the end-product and the reaction does not necessarily stop at the dimer stage but can be continued to form a trimer derivative which finally leads to a polymer resin.



The aforesaid proves that the process described in document D1 is unsuitable for the preparation of our compound of the Formula I. This is further substantiated by the fact that in document D1 by the above method no compound of the general Formula I, in which R₁ stands for hydrogen, has been prepared by reacting a compound of the general Formula V with a compound of the general Formula VII.

In the present patent application as an example this reaction has been disclosed. We have succeeded in suppressing the self-alkylation reaction and obtaining the tertiary amine selectively with excellent yields. It could not be foreseen that the reaction could be carried out in such a selective manner because according to prior art the N-2 nitrogen can be easily alkylated.

Our recognition is so much the more surprising as it has been disclosed in prior art [e.g. Cho Su-Dong et al: J. Het. Chem., 35, 3, 601-606 (1998)] that 4,5-dichloro-pyridazine-3-one can be alkylated on the N-2 nitrogen atom of the

pyridazine ring with benzyl chloride in a dipolar aprotic solvent in the presence of potassium carbonate at 50°C with benzyl chloride with a yield of 92 %.



It is also known [T. Nakagome et al: Chem. Pharm. Bull. (Tokyo), 14, 1090 (1966)] that alkylation of pyridazine-3-one-derivatives takes place on the N-1 nitrogen atom of the pyridazine ring under formation of a quaternary salt.

Thus it is surprising and unforeseen that according to the present invention substitution of the N-2 nitrogen atom of the pyridazine ring and quaternisation of N-1 nitrogen atom of the pyridazine ring could be avoided and the desired end-product can be prepared by reacting compounds of the general Formulae II and VI in a selective manner with high yields.

2) Reaction variants b₃ and b₄

According to these reaction variants a compound of the general Formula VII is reacted with a compound of the Formula VI to give a compound of the Formula VIII.

It is surprising that the secondary amine of the Formula VI reacts **selectively** only with the carbon atom bearing the X leaving group while the chlorine atom in position 3 of the pyridazine ring is not substituted. There are several examples in prior art which would lead the skilled out worker to the presumption that the chlorine atom in position 3 would be substituted. Thus reference is made to D. K. Chesney et al [J. Het. Chem., 11, 167 (1974)] wherein it is described that if 4-amino-3,5-dichloro-pyridazine-3-one is reacted

with methyl hydrazine substitution takes place in position 3 of the pyridazine ring.

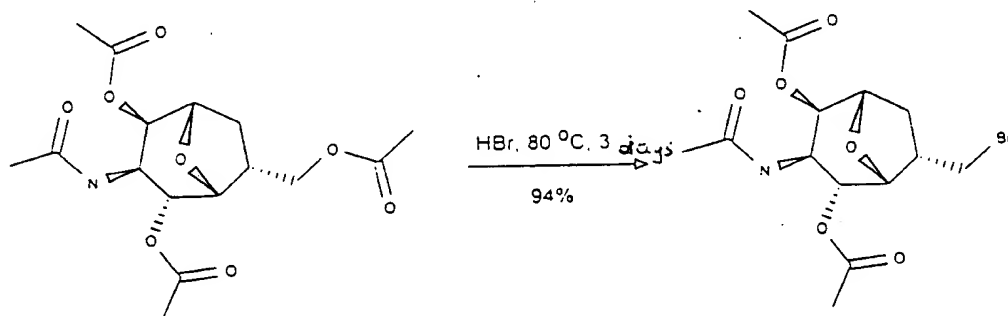
ii.

The Examiner states that reaction variants a_2 - a_3 and b_4 are known methods for the transformation of an ester group into a more suitable leaving group.

1) Reaction variants a_2 and a_3

In the case of the starting materials of the general Formula III of the present patent application it could not be unforeseen that two leaving groups (one on the nitrogen and one on the oxygen) can be removed simultaneously in such a manner that at the same time the new leaving group X is formed at the end of the chain. It is highly surprising that the reaction can be carried out with good yields.

It is namely known from prior art [Ogawa et al: Carbohydr. Res., 194, 115-124 (1989)] that on reacting the following N,O-diacetyl derivative with hydrogen bromide at 80°C for 3 days the corresponding N-acetyl-bromo derivative is obtained with the yield of 94 %.



It can be seen that in a reaction of the similar type the N-acetyl group remained unchanged while simultaneously the O-acetyl group was selectively converted into the bromo derivative.

Taking into consideration the teaching of prior art it is surprising and unaforeseen that according to the present invention a compound of the general Formula II can be prepared from a compound of the general Formula III in one step with high yields.

2) Reaction variant b₄

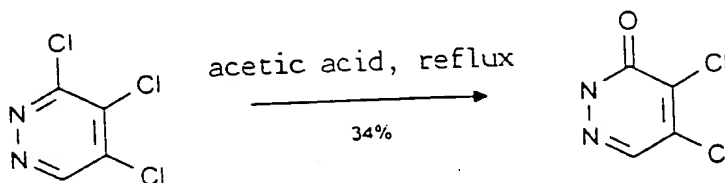
According to this process the compound of the Formula VIII can be prepared from the compound of the Formula IV surprisingly in a uniform manner. This is surprising and unaforeseen because it is known from prior art that bromo-propyl-amino derivatives are easily converted under heating into azetidinium bromides. However, it has been surprisingly found in the case of the present invention that the compound of the Formula VII is obtained in a selective manner.

III.

The Examiner has stated that reaction variants a₂ and b₂-b₄ relate to well known methods for the conversion of a 3-pyridazine into a 3-pyridazinone.

1) Reaction variant a₂

It is known that re-conversion of 1-halogen-pyridazine into 3-pyridazinone is possible. However, even in such a simple case as 3,4,5-trichloro-pyridazine the corresponding pyridazinone can be obtained in acetic acid only with a yield of 34 % [T. Kuraishi: Chem. Pharm. Bull. (Tokyo), 5, 376 (1957)].



It has been surprisingly found that the reaction can be carried out with such a high yield.

In the case of the present patent application the formation of a N,O-diacyl-derivative of the general Formula III could not be unforeseen because when using the other regioisomer under similar reaction conditions only the O-acyl derivative is formed. In case of the desired 4-substituted isomer the importance of the diacyl derivative obtained is increased by the fact that the diacyl derivative is an extremely well crystallizable compound and can be separated from the undesired 5-isomer (this is a mono-O-acyl derivative) by simple recrystallization at this stage. This recognition is completely unexpected in view of the teaching of prior art.

2) Reaction variants b₂-b₄

In view of the aforesaid it could not be unforeseen that in course of transformation of pyridazine into pyridazinone the N-acetyl derivative is formed.

IV.

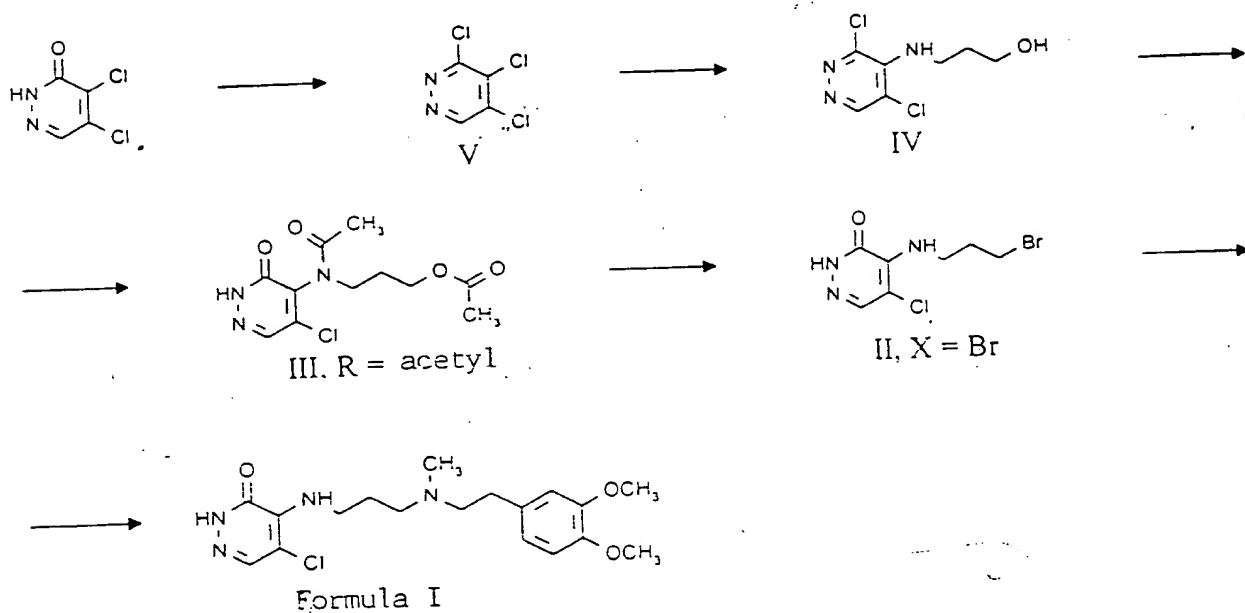
The Examiner states that reaction variants b₁-b₄ are known methods for desacetylation of a N-acetyl compound.

While prior art contains numerous examples for the desacetylation of secondary amines, when carrying out the reaction with 48 % aqueous hydrogen as performed in the case of the present invention, according to prior art desacetylation does not always take place. It is namely disclosed in prior art [e.g. Ogawa et al: Carbohydr. Res., 194, 115-124 (1989)] that on reacting a N-acetyl-derivative with hydrogen bromide at 80°C for 3 days the N-acetyl group remained practically unchanged and could not be split off.

On the other hand it has been found in a surprising way that according to the process of the present invention desacetylation with hydrogen bromide actually takes place, contrary to the disclosure of the prior art.

V.

The best form of realization of the process of the present invention is shown in the following reaction scheme.



It is to be emphasized that intermediates of the Formulae IV, III (R is e.g. acetyl) and II (X is e.g. bromine) are new compounds, never described in prior art. These intermediates are inventive because they can be converted into the pharmaceutically active end-product of the Formula I with such excellent yields and in such a preferably way which could not be unforeseen in prior art.

As a summary it can be stated that the present invention is both novel and inventive.

A favourable reconsideration of the Written Opinion is respectfully requested.

Budapest, August 9, 2000

Respectfully submitted

Béla Karácsonyi
Patent Attorney for Applicant